REMARKS

Amendments

Claims 1-25 are pending upon entry of this amendment. Claims 1-7, 9 and 11-16 have been withdrawn, claims 8, 10 and 17 have been amended, and claims 18-25 have been added. The amendment does not constitute new matter and is supported throughout the specification and claims as originally filed. With regard to the term "null allele", Applicant respectfully submits that one of skill in the art would understand the definition of "disruption" on page 6, line 26 to page 7, line 3, to encompass the art recognized term "null allele". Accordingly, no new matter is introduced. Applicant submits that new claims 18-25 fall within the scope of the elected claims.

Rejections

Rejections under 35 U.S.C. § 101

Claims 8, 10 and 17 stand rejected as the claimed invention allegedly is not supported by either a specific or substantial asserted utility or a well-established utility. The independent claim 8 is generally directed to a transgenic mouse comprising a null Cer1 allele. The Examiner essentially argues that the claimed mice do not have a specific, substantial, credible, or well-established utility. For example, the Examiner alleges that: (i) the claimed mice do not have utility as a model for disease; (ii) using the mice to identify agents capable of altering a phenotype is not a "specific utility"; and (iii) the claimed mice may not be capable of being used to determine the function of Cer1(page 6). Applicant respectfully traverses the rejection.

1. The Utility Requirement

According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.
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> . . .
>
> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion

> would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)).

The standard for "credible" is defined as:

> . . . whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

(MPEP 2107.02, III(B)(emphasis added).

According to the Patent Office's own guidance to Examiners:

> **Rejections under 35 U.S.C. 101 have been rarely sustained by federal courts**. Generally speaking, in these rare cases, the 35 U.S.C. 101 rejection was sustained either because the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967). Special care therefore should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, of the absence of a proven animal model for testing the effectivenss of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under 35 U.S.C. 101.

(MPEP 2107.02, III(B)(emphasis in original and added). The Guidelines additionally provide that:

> There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather, the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed (citations omitted), and whether the asserted utility appears to contravene established scientific principles and beliefs. (citations omitted). Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." (citations omitted). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980)(reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court pointed out that a rigorous correlation is not necessary when the test is reasonably predictive of the response).

(MPEP 2107.02, VII)(emphasis added).

Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose. The present invention satisfies either standard.

2. The Claimed Subject Matter Has Well-Established Utility

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined.

According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
>
> . . .
>
> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834)(emphasis added)(copy attached). Thus, the knockout mouse has been accepted by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible.

Knockout mice are so well accepted as tools for determining gene function that the director of the NIH Chemical Genomics Center of the National Human Genome Research

Institute (among others, including Capecchi, Bradley, Joyner, Nagy and Skarnes) has proposed creating knockout mice for all mouse genes:

> Now that the human and mouse genome sequences are known, attention has turned to elucidating gene function and identifying gene products that might have therapeutic value. The laboratory mouse (Mus musculus) has had a prominent role in the study of human disease mechanisms throughout the rich, 100-year history of classical mouse genetics, exemplified by the lessons learned from naturally occurring mutants such as agouti, reeler and obese. The large-scale production and analysis of induced genetic mutations in worms, flies, zebrafish and mice have greatly accelerated the understanding of gene function in these organisms. Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.
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> . . .
>
> A coordinated project to systematically knock out all mouse genes is likely to be of enormous benefit to the research community, given the demonstrated power of knockout mice to elucidate gene function, the frequency of unpredicted phenotypes in knockout mice, the potential economies of scale in an organized and carefully planned project, and the high cost and lack of availability of knockout mice being made in current efforts.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 921)(emphasis added)(copy attached).

With respect to amended claims drawn to transgenic mice having a null allele, the following comments from Austin are relevant:

> **Null-reporter alleles should be created**
>
> The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point for studying the function of every gene. Inserting a reporter gene (e.g., P-galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normally support the expression of that gene.

(p. 922)(emphasis added).

According to the Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)), one of the leading textbooks in the field of molecular biology:

> Extensive collaborative efforts are underway to generate comprehensive libraries of mutation in several model organisms including . . . the mouse. The ultimate goal in each case is to produce a collection of mutant strains in which every gene in the organism has

> either been systematically deleted, or altered such that it can be conditionally disrupted. Collections of this type will provide an invaluable tool for investigating gene function on a genomic scale.
>
> (p. 543)(emphasis added).

According to Genes VII (Lewin, Oxford University Press (2000)), another well respected textbook in the field of genetics:

> The converse of the introduction of new genes is the ability to disrupt specific endogenous genes. Additional DNA can be introduced within a gene to prevent its expression and to generate a null allele. Breeding from an animal with a null allele can generate a homozygous "knockout", which has no active copy of the gene. This is a powerful method to investigate directly the importance and function of the gene.
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> (p. 508)(emphasis added).

According to Joyner (Gene Targeting: *A Practical Approach*, Oxford University Press 2000):

> Gene targeting in ES cells offers a powerful approach to study gene function in a mammalian organism.
>
> (preface)(emphasis added).

According to Matise et al. (*Production of Targeted Embryonic Stem Cell Clones* in Joyner, Gene Targeting: *A Practical Approach*, Oxford University Press 2000):

> The discovery that cloned DNA introduced into tissue culture cells can undergo homologous recombination at specific chromosomal loci has revolutionized our ability to study gene function in cell culture and *in vivo*. . . . Thus, applying gene targeting technology to ES cells in culture affords researchers the opportunity to modify endogenous genes and study their function *in vivo*.
>
> (p. 101)(emphasis added).

According to Crawley (What's Wrong With My Mouse *Behavioral Phenotyping of Transgenic and Knockout Mice*, Wiley-Liss 2000):

> Targeted gene mutation in mice represents a new technology that is revolutionizing biomedical research.
>
> Transgenic and knockout mutations provide an important means for understanding gene function, as well as for developing therapies for genetic diseases.
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> (p. 1, rear cover)(emphasis added).

Research tools such as knockout mice are clearly patentable, as noted by the Patent Office:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function).

For example, according to Crabbe *et al.* (Science (1999) 284:1670-1672) *a reference cited by the Examiner*), "[t]argeted and chemically induced mutations in mice are valuable tools in biomedical research." As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function).

Applicant submits that since one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, a utility that is specific, substantial and credible, the invention has a well-established utility, thus satisfying the utility requirement of section 101. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

3. The Claimed Subject Matter is Useful for A Particular Purpose

In addition, the claimed invention is useful for a particular purpose. The Applicant has demonstrated and disclosed specific phenotypes of the presently claimed mice, i.e., increased anxiety. Utility of the claimed knockout mouse would be apparent to, and considered credible

by, one of skill in the art, as the role of knockout mice in studying the anxiety is both specific and substantial.

The claimed knockout mouse demonstrates a role for the target gene in anxiety disorders. Therefore, the target gene correlates with a specific disorder. Anxiety disorders are a well-recognized condition which are the subject of drug development studies and treatment strategies. For example, there are currently in excess of sixty (60) clinical trials enrolling patients for the study of anxiety disorders (http://clinicaltrials.gov/ct/screen/BrowseAny?path=%2Fbrowse%2Fby-condition%2Faz%2FA%2FD001008%2BAnxiety%2BDisorders&recruiting=true). The broad interest in studying treatments for anxiety disorders establishes that the phenotype and the disease/disorder are one and the same. Further establishment of a correlation between the phenotype and the disease/disorder is unnecessary and unwarranted.

In addition, the utility of a knockout mouse demonstrating increased anxiety has been recognized as a useful tool in the discovery of anxiolytics. For example, Mombereau *et al.* (*Neuropsychopharmacology* (2004) 29, 1050-62) discloses a $GABA_B$ receptor knockout having increased anxiety:

> Recently, we demonstrated that mice lacking the GABA(B(1)) subunit were more anxious than wild-type animals in several behavioural paradigms, most notably in the light-dark test. In an attempt to assess the effects of classical benzodiazepine anxiolytics on anxiety-like behaviour observed in these mice, animals were administered either chlordiazepoxide (10 mg/kg, p.o.) or diazepam (7.5 mg/kg, p.o.) prior to testing in the light-dark box. Surprisingly, in contrast with the wild-type mice, neither benzodiazepines decreased anxiety-like behaviour in GABA(B(1))(-/-) mice. These data suggest that targeted deletion of GABA(B(1)) subunit alters GABA(A) receptor function in vivo.

(abstract)(emphasis added)(http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15321743). Based on observations in the knockout mouse and subsequent pharmacological experiments using receptor antagonists, the authors proposed that the $GABA_B$ receptor serve as a novel therapeutic strategy for the development of anxiolytics.

In another example, Lewejohann et al., (*Behav Brain Res.* (2004) 23;154(1):273-89) observed increased anxiety in BC1 deficient mice:

> BC1 RNA is a small non-messenger RNA common in dendritic microdomains of neurons in rodents. In order to investigate its possible role in learning and behaviour, we compared controls and knockout mice from three independent founder lines established from separate embryonic stem cells. Mutant mice were healthy with normal brain morphology and appeared to have no neurological deficits. A series of tests for exploration and spatial memory was carried out in three different laboratories. The tests were chosen as to ensure that different aspects of spatial memory and exploration could be separated and that possible effects of confounding variables could be minimised. Exploration was studied in a barrier test, in an open-field test, and in an elevated plus-maze test. Spatial memory was investigated in a Barnes maze and in a Morris water maze (memory for a single location), in a multiple T-maze and in a complex alley maze (route learning), and in a radial maze (working memory). In addition to these laboratory tasks, exploratory behaviour and spatial memory were assessed under semi-naturalistic conditions in a large outdoor pen. The combined results indicate that BC1 RNA-deficient animals show behavioural changes best interpreted in terms of reduced exploration and increased anxiety. In contrast, spatial memory was not affected. In the outdoor pen, the survival rates of BC1-depleted mice were lower than in controls. Thus, we conclude that the neuron-specific non-messenger BC1 RNA contributes to the aptive modulation of behaviour.

(abstract)(emphasis added)(
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15302134).

In yet a further example, Haller et al. (*Behav Pharmacol.* (2004) 15(4):299-304) compared the effect of agents on CB1 deficient mice with wild-type controls:

> Cannabinoids are known to modulate GABAergic and glutamatergic transmission in cortical areas, the former via CB1 and the latter via a novel receptor. Pharmacological data demonstrate that several widely used cannabinoid ligands bind to both receptors, which may explain the inconsistencies in their behavioural effects. Earlier we showed that the cannabinoid antagonist SR-141716A affected behaviour in both CB1 knockout and wild-type animals, and its effect (anxiolysis) was different from that of CB1 gene disruption (anxiogenesis). In the present experiments, we studied the effects of the CB1 antagonist AM-251, and the cannabinoid agonist WIN-55,212-2 in wild-type as well as in CB1 knockout mice. CB1 knockout mice showed higher scores of anxiety-like behaviour than the wild-type animals in the elevated plus-maze. Selective blockade of CB1 receptors by AM-251 (0.3, 1 and 3 mg/kg) increased anxiety-like behaviour dose-dependently in the wild-type mice but had no effect in the knockouts. In wild types, the cannabinoid agonist WIN-55,212-2 (1 and 3 mg/kg) caused a decrease in anxiety-like behaviour, which was abolished by the CB1-selective antagonist AM-251 (3 mg/kg). The same agonist did not change plus-maze behaviour in CB1 knockout animals. These data demonstrate at the behavioural level that AM-251 and, at low concentrations, WIN-55,212-2, are selective ligands of the CB1 cannabinoid receptor in mice. Our studies on the behavioural effects of the cannabinoid antagonist SR-141716A and the CB1

> antagonist AM-251 show that the CB1 and the novel cannabinoid receptor mediate anxiolytic and anxiogenic effects, respectively. This suggests that agonists of the former, or antagonists of the latter, are promising new compounds in the pharmacotherapy of anxiety.

(abstract)(emphasis added)(http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15252281). The above-cited references clearly demonstrate that one skilled in the art recognizes the utility of transgenic mice demonstrating anxiety related phenotypes, including in drug development studies.

The Examiner argues that the Applicant has not established a link between the recited phenotypes and the gene in humans. The Examiner's arguments are similar to arguments made by the Patent Office with respect to pharmaceutical compounds the utility of which were based on murine model data, arguments which were dismissed by the Federal Circuit in *In re Brana* (34 U.S.P.Q.2d 1436)(Fed. Cir. 1995). The case involved compounds that were disclosed to be effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The court ruled that the PTO had improperly rejected, for lack of utility, claims for pharmaceutical compounds used in cancer treatment in humans, since neither the nature of invention nor evidence proferred by the PTO would cause one of ordinary skill in art to reasonably doubt the asserted utility.

The first basis for the Board's holding of lack of utility (the Board adopted the examiner's reasoning without any additional independent analysis) was that the specification failed to describe any specific disease against which the claimed compounds were useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. (*In re Brana* at 1439-40). The Federal Circuit reasoned that the leukemia cell lines were originally derived from lymphocytic leukemias in mice and therefore represented actual specific lymphocytic tumors. The court concluded that the mouse tumor models represented a specific disease against which the claimed compounds were alleged to be effective. (*In re Brana* at 1440).

The Board's second basis was that even if the specification did allege a specific use, the applicants failed to prove that the claimed compounds were useful.

The Federal Circuit responded: "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (*Brana* at 1441, *citing In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)). From this it followed that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. (*Id.*)

The court held that the Patent Office had not met its burden. The references cited by the Board did not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, the references merely discussed the therapeutic predictive value of *in vivo* murine tests -- relevant only if the applicants were required to prove the ultimate value in humans of their asserted utility. The court did not find that the nature of the invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. The purpose of treating cancer with chemical compounds did not suggest an inherently unbelievable undertaking or involve implausible scientific principles. (*Id.*)

The Court concluded that one skilled in the art would be without basis to reasonably doubt the asserted utility on its face. The PTO had not satisfied its initial burden. Accordingly, the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. (*Id.*)

As in *Brana*, Applicant has asserted that the claimed invention is useful for a particular practical purpose, an assertion that would be considered credible by a person of ordinary skill in the art. As discussed above, the claimed mice have demonstrated specific phenotypes. The acceptance among those of skill in the art of knockout mice demonstrating such properties is clearly demonstrated.

Definitive proof that the phenotypes observed in the null mouse would be the same as those observed in humans is not a prerequisite to satisfying the utility requirement. It is enough

that the claimed mouse demonstrates phenotypes, relative to a wildtype control mouse, and that knockout mice are recognized in the art as models for determining gene function. As noted by Austin et al.:

> Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.

(p. 921)(emphasis added).

In addition, as pointed out by Doetschman, one clearly skilled in the art, (*Laboratory Animal Science* 49:137-143, 137 (1999)(copy attached), the phenotypes observed in mice do correlate to gene function:

> The conclusions will be that the knockout phenotypes do, in fact, provide accurate information concerning gene function, that we should let the unexpected phenotypes lead us to the specific cell, tissue, organ culture, and whole animal experiments that are relevant to the function of the genes in question, and that the absence of phenotype indicates that we have not discovered where or how to look for a phenotype.

(emphasis added).

In *Brana*, the claimed compound had demonstrated activity against a murine tumor implanted in a mouse. Yet, the Federal Circuit found that utility had been demonstrated. Here, the invention relates to a disruption in a murine gene in a mouse. Like the tumor mouse model, the knockout mouse with a specific gene disrupted is a widely accepted model, the utility of which would be readily accepted in the art. It is submitted that one skilled in the art would be without basis to be reasonably doubt Applicant's asserted utility, and therefore the Examiner has not satisfied the initial burden.

It is respectfully submitted that the utility of the claimed mice does not rest solely on whether the claimed mice can conclusively establish the function of the targeted gene. Applicant is claiming a knockout mouse. The burden should not be placed on Applicant to establish that mutations in the human homolog of the Cer1 gene result in the same phenotypes observed in mice. This task is more appropriately placed on the commercial and academic entities conducting further research using the present invention as a tool. As noted by the Federal

Circuit, usefulness in patent law necessarily includes the expectation of further research and development. (*In re Brana* at 1442).

The Examiner also questions the veracity of the conclusions reached by Applicant with respect to the phenotypic data. The Examiner states that one of ordinary skill would have been critical of the data in the specification. Applicant submits that all of the pathological, physiological and behavioral observations and conclusions based thereon which are set forth in the specification were made by highly skilled pathologists and behavioral specialists. The conclusion that the claimed mice exhibit increased anxiety is based on observations of a decrease in average velocity during episodes of movement, decrease in total distance traveled, and an increase in the number of fecal boli. Applicant's conclusions are reasonable. It is also submitted that the Examiner is misreading the data table: the number of mice is set forth under the "count" column. Each row of Table 1 represents the data obtained from 10 or 9 as indicated under the "count" column. Comparison of row 1 with row 3 reveals a statistically significant decrease in total travel.

The Examiner argues that using the claimed mice as a tool for defining the function and role of the disrupted gene does not establish utility because such a use rises merely to the level of scientific utility, but does not rise to the level of a specific, substantial and credible utility. Applicant respectfully disagrees. The use of the claimed mouse to investigate the function of the Cer1 gene is specific because only the Cer1 gene is disrupted. Moreover, the claimed mouse was not randomly mutagenized; rather, the Cer1 gene was specifically targeted to created the claimed mouse. Finally, the claimed mouse is uniquely suited for investigating the Cer1 gene because only the Cer1 gene is disrupted in the claimed mouse. Therefore, Applicant submits that the claim subject matter has specific utility.

The claimed mice have substantial utility because the claimed mice a real world use. The mice are commercially available for studies relating to the Cer1 gene. Moreover, as noted above, knock-out mice in general have real world use because knock-out mice are routinely used to develop new treatments. Applicants submit that the mouse itself is not studied, but rather, the effects of the disrupted gene is studied. The claimed mice have a credible utility because it is well-known in the art to use knock-out mice for investigating the function of a targeted gene.

The Examiner argues that the claimed mice may not be capable of determining the function of the gene. Applicant respectfully points out that **humans** determine the function of a

gene using tools such as the claimed mice. The fact that in the opinion of the Examiner a human may not be readily able to ascertain the function of the gene **using** the claimed mice does not negate the fact that the mice are useful for that very purpose. Because one may not know how to use a tool does not mean the tool is unpatentable. Applicant respectfully submits that the references cited herein amply establish that those of skill in the art know how to use the claimed mice. Moreover, Applicant respectfully submits that so long as the claimed mice can be used to obtain data related to the function of the targeted gene as taught by the specification, the claimed mice have patentable utility.

With regard to the Examiner's assertion that significant further research would be required to determine the function of the cerebus gene, Applicant points out the claims do not require that function of the cerebus gene be determined. Applicant respectfully submits that the issue of additional research relates to enablement and not to utility. The determination of utility must be made with regard to claimed subject matter. Because the claims do not require the determination of the function of the cerebus gene, whether or not additional research is required to determine the function of the cerebus gene is irrelevant to the determination of utility.

In summary, Applicant submits that the claimed Cer1 gene knockout mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the Cer1 gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the specific phenotypes of the transgenic mice demonstrate that the mice are useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly established a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant would be specific and substantial. (*In re Brana*; MPEP § 2107). Withdrawal of the rejections under section 101 is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 8, 10, and 17 because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility for the reasons set forth in the utility rejection. Applicants respectfully traverse the rejection. For the reasons set forth above,

the claimed invention satisfies the utility requirement. Therefore, one skilled in the art would know how to use the invention. Applicant respectfully requests withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 10 and 17 are rejected as allegedly indefinite. Claim 10 is rejected because a pseudopregnant mouse does not give birth. Applicant has amended the claim to recited that the blastocyst develops into a chimeric mouse. In view of the amendment, the rejection is overcome.

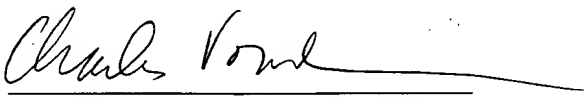
Claim 17 is rejected because the term "anti-depressive" behavior is allegedly unclear. Applicant has amended the claim to clarify that the claim mouse shows a decreased susceptibility to depression. Basis for this amendment is found, for example, on page 51, lines 15-17. Accordingly, no new matter is introduced.

Conclusion

In view of the above amendments and remarks, Applicant respectfully requests reconsideration and a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

In the event a petition for an extension of time is required, this paper is to be considered such a petition. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,



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